Current Treatments for the Coronavirus (COVID-19)

Inpatient Treatments for COVID-19

Remdesivir: *200mg IV x 1 day, followed by 100mg IV for 4 days*

Mechanism of Action: Disrupts the virus' ability to multiply and infect more cells in the body. It does so through inhibition of viral replication through premature termination of RNA transcription. Its use can improve disease outcomes and reduce viral loads.[1]

Clinical Trial: In the ADAPTIVE COVID-19 trial, a multinational, randomized controlled trial that compared remdesivir to placebo, patients with moderate symptomology had greater clinical status later in disease when compared to placebo, and improved time to recovery. There was no observed benefit in patients not requiring supplemental oxygen, mechanical ventilation, or ECMO.[2]

Recommendations: NIH/IDSA guidelines recommend 200mg IV for 1 day, followed by 100mg IV for 4 days, or until hospital discharge, whichever comes first.[1,3] WHO guidelines recommend against routine use – the evidence from their meta-analyses suggested no benefit.[4]

Duration of Treatment: In a recent open-label trial supported by Gilead Sciences, there was no significant difference in efficacy between 5 and 10 day courses, so patients should be limited to 5 day courses.[5]

Overall, it appears remdesivir does not provide an overall mortality benefit, but that it does reduce time to clinical improvement when given early in the course of illness and/or in patients with less severe disease. Duration of treatment between 5 and 10 day courses did not show a significant difference in efficacy. In crisis capacity settings with limited remdesivir supply, remdesivir appears to demonstrate the most benefit in those with severe COVID-19 on supplemental oxygen rather than in patients on mechanical ventilation or ECMO.

Dexamethasone: *6mg IV/PO daily for up to 10 days*

Mechanism of Action: potent corticosteroid with predominately glucocorticoid effects and little to no mineralcorticoid action that increases the production of anti-inflammatory compounds and reduces the production of pro-inflammatory compounds.[1]

Clinical Trial: In the RECOVERY trial, those with moderate-severe disease (requiring supplemental oxygen, mechanical ventilation, or ECMO) had reduced mortality at 28 days than patients randomized to the standards of care; the greatest evidence was seen for those on MV. Among participants who did not require supplemental oxygen at enrollment there was statistically insignificant higher mortality associated.[5]

Recommendations: NIH/IDSA guidelines recommend dexamethasone IV/PO 6mg daily for up to 10 days.[1,3] WHO guidelines recommend dexamethasone 6mg QD for 7-10 days OR 50mg of hydrocortisone IV q8hrs for 7-10 days.[7]

Duration of Treatment: Extended treatment should not be preferred as it inhibits the protective function of T cells and blocks B cells from making antibodies, leading to prolonged increases in plasma viral load. Dexamethasone's half-life is 36-48 hours so dosing is only once daily.[8]

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Overall, it appears dexamethasone provides an overall mortality benefit, with the most prominent benefits seen in those on mechanical ventilation. Dexamethasone can be administered IV or PO at 6mg daily for up to 10 days; extended treatment may prolong elevated plasma viral load. There was a trend (though statistically insignificant) towards higher morality when utilized in patients NOT requiring oxygen therapy.

Tocilizumab: *8mg/kg (actual body weight) IV x 1 (max dose = 800mg)*

Mechanism of Action: interleukin-6 receptor antagonist that inhibits the release of cytokines and the associated pro-inflammatory state.[1]

Clinical Trial: In the COVACTA trial, 450 adults hospitalized with severe COVID-19-related pneumonia were randomized to receive tocilizumab or placebo. The trial failed to meet its primary endpoint or several key secondary endpoints including a lack of any mortality benefit, need for ICU care and/or ventilator use, and supplemental oxygen requirements.[9]

Recommendations: IDSA/NIH no longer recommends using tocilizumab unless under a clinical trial.[1,3]

Overall, it appears tocilizumab has minimal benefit in the treatment of COVID-19. The medication is extremely costly and is no longer recommended in any major guideline treatment algorithm.

Convalescent Plasma: *neutralizing antibody titers of at least 1:160*

Mechanism of Action: provides passive immunotherapy via pathogen neutralization; CP, which includes antibodies, is derived from people who have recovered from COVID-19. Postulated to have direct antiviral properties in those with active infection, reducing viral load.[1]

Clinical Trial: CP lacks sufficient data from well-controlled randomized clinical trials. Both the FDA and Mayo Clinic have performed retrospective, indirect evaluations of efficacy and have hypothesized that patients who received plasma units with higher titers of SARS-CoV-2 neutralizing antibodies would have better clinical outcomes. There is still no standardization established for screening of donated CP, and oftentimes assays to assess titer quantity are not widely available. Use in expanded access programs often do not assess titer quantity prior to infusion.[1]

Recommendations: IDSA recommends limiting the use of CP for patients admitted to the hospital to the context of a clinical trial.[3] NIH states insufficient data to recommend either for or against the use.[1] CP is often not routinely stocked at hospitals and can take up to 24 hours to obtain, and any patient who receives CP should receive anticoagulation with enoxaparin.[3]

Overall, CP lacks sufficient data for use and efficacy is limited to titer quantity, which is often not assessed prior to infusion. Many institutions have utilized through EUA or clinical trials. Any patient who receives CP should, at a minimum, receive intermediate dose prophylaxis with enoxaparin.

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Antithrombotic Therapy: *UF, LMWH, DOACs, or Warfarin* therapy + Aspirin*

Mechanism of action: COVID-19 has been associated with inflammation and a prothrombotic state, with increases in fibrin, fibrin degradation products, fibrinogen, and d-dimers, and thus has been associated with increases in DVT and stroke risk.[1]

Recommendations

All adults who are admitted should receive VTE prophylaxis (UF, LMWH, DOACs, Warfarin*) in addition to ASA 81mg. Warfarin is not evidenced in anticoagulation recommendations due to lack of evidence. Many clinicians still feel comfortable utilizing as long as INR and d-dimer are stabilized. If multiple doses are being held due to high/unstable INR, conversion to UF or DOACs are reasonable considerations. UF and LMWH are the preferred agents as they are easy to reverse, have a short half life, and minimal drug-drug interactions.[1]

Overall, all adults who are admitted should receive VTE prophylaxis, in addition to ASA 81mg. UF and LMWH are the preferred agents as they are easy to reverse, have a short half-life, and have minimal drug-drug interactions, though DOACs may also be utilizes. Warfarin is not evidenced in anticoagulation recommendations due to lack of evidence, though may clinicians feel comfortable with its use as long as the INR and d-dimer remain stabilized and doses are not routinely held.

Baricitinib (with remdesivir): *adults and pediatric patients (9+ years old): 4mg daily; pediatric pts (2-9 years old): 2mg daily*

Mechanism of Action: Janus kinase inhibitors are potent immunosuppressive agents, which interfere with phosphorylation of signal transducer and activator of transcription (STAT) proteins that are involved in vital cellular functions, including signaling, growth, and survival. This prevents the signal transduction that leads to immune activation and inflammation (e.g., the cellular response to proinflammatory cytokines such as interleukin [IL]-6). Baricitinib also has theoretical direct antiviral activity through interference with viral endocytosis, potentially preventing entry into and infection of susceptible cells.[10]

Clinical Trials: Combination of remdesivir & baricitinib was shown to reduce time to recovery within 29 days after initiating treatment compared to patients who received remdesivir alone. The odds of a patient's condition progressing to death or being ventilated at day 29 was also lower in the baricitinib group. The median time to recovery was 7 days, versus 8 days with remdesivir alone.[10]

Recommendation: FDA issued an EUA for the drug baricitinib, in combination with remdesivir, for treatment of COVID-19 in hospitalized patients (2 years and older) requiring supplemental oxygen, ECMO, or mechanical ventilation. Dosing is 4mg daily for those 9+ years old and 2mg daily for those <9 years old.[11] IDSA/NIH/WHO guidelines have not yet updated their guidelines to recommend for/against use.

Overall, baricitinib, in combination with remdesivir, may reduce time to recovery and reduce progression to death or requiring mechanical ventilation. Use has not been evaluated by major guidelines, though the FDA has issued an EUA for use in hospitalized patients requiring supplemental oxygen, ECMO, or mechanical ventilation.

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Outpatient Treatments for COVID-19: Monoclonal Antibodies

Bamlanivimab: *700mg IV infusion once over 60 minutes*

Mechanism of Action: Monoclonal antibodies are laboratory-made proteins that mimic the immune system's ability to fight off harmful antigens. Bamlanivimab is a mAb that is specifically directed against the spike protein of SARS-CoV-2, designed to block the virus' attachment and entry into human cells.[12]

Clinical Trial: In BLAZE-1, a phase two randomized, double-blind, placebo-controlled clinical trial, 465 non-hospitalized adults with mild to moderate COVID-19 symptoms received either bamlanivimab (309 patients) or placebo (156 patients within three days of obtaining a COVID+ result. The most important evidence that bamlanivimab may be effective came from the predefined secondary endpoint of COVID-19-related hospitalizations or emergency room visits within 28 days after treatment. For patients at high risk for disease progression, hospitalizations and emergency room visits occurred in 3% of bamlanivimab-treated patients on average compared to 10% in placebo-treated patients.[12]

Recommendation: FDA issues an EUA for the treatment of mild-to-moderate COVID-19 in adult and pediatric patients (12 and up, ≥40kg) who are not currently hospitalized or requiring supplemental oxygen and who are at high risk of progressing to severe COVID-19 and/or hospitalization (those 65+ years old and/or who have certain chronic medical conditions). The effects on viral load and on reduction in hospitalizations and ER visits, and on safety, were similar in patients receiving any of the three bamlanivimab doses, so the lowest dose, 700mg IV, is recommended.[13]

Casirivimab & Imdevimab: *1,200mg of each mAb in a single IV infusion over 60 minutes*

Mechanism of Action: Casirivimab and imdevimab are monoclonal antibodies that are specifically directed against the spike protein of SARS-CoV-2, designed to block the virus' attachment and entry into human cells.[14]

Clinical Trial: In R10933-10987-COV-2067, a randomized, double-blind, placebo-controlled clinical trial, 799 non-hospitalized adults with mild to moderate COVID-19 symptoms received either casirivimab/imdevimab (533) or placebo (266). Viral load reduction in patients treated with casirivimab and imdevimab was larger than in patients treated with placebo at day 7. Predefined secondary endpoint of medically attended visits related to COVID-19, particularly hospitalizations and emergency room visits within 28 days after treatment, showed that for patients at high risk for disease progression, hospitalizations and emergency room visits occurred in 3% of casirivimab and imdevimab-treated patients on average compared to 9% in placebo-treated patients.[14]

Recommendation: FDA issued an EUA for casirivimab and imdevimab to be administered together for treatment of mild-to-moderate COVID-19 in adults and pediatric patients (12 and up, ≥40kg) who are at high risk for progressing to severe COVID-19 (those 65+ years old and/or who have certain chronic medical conditions). The authorized dosage is 1,200 mg of casirimab and 1,200 mg of imdevimab administered in a single infusion over 60 minutes.[15]

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